http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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L2            0 US20060016033/PN

=> s us20060106033/pn
L3            1 US20060106033/PN

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L3   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2009 ACS on STN
RN   30413-58-2P
RN   656800-40-7P
RN   672932-47-7P
RN   672932-48-8P
RN   672932-49-9P
RN   672932-46-6P
RN   672932-50-2P
RN   672932-51-3P
RN   672932-52-4P
RN   672932-53-5P
RN   672932-54-6P
RN   672932-55-7P
RN   672932-56-8P
RN   108-24-7
RN   1066-54-2
RN   1188-33-6
RN   5315-25-3
RN   6295-87-0


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               672932-52-4/BI OR 672932-53-5/BI OR 672932-54-6/BI OR 672932-55-
               7/BI OR 672932-56-8/BI)

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L4   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2007:188039  CAPLUS
DOCUMENT NUMBER:         146:421892
TITLE:                   Synthesis and biological evaluation of fenobam analogs
                         as mGlu5 receptor antagonists
AUTHOR(S):               Jaeschke, Georg; Porter, Richard; Buettelmann, Bernd;
                         Ceccarelli, Simona M.; Guba, Wolfgang; Kuhn, Bernd;
                         Kolczewski, Sabine; Huwyler, Joerg; Mutel, Vincent;
                         Peters, Jens-Uwe; Ballard, Theresa; Prinssen, Eric;
                         Vieira, Eric; Wichmann, Juergen; Spooren, Will
CORPORATE SOURCE:        Discovery Research, Pharmaceutical Division, F.
                         Hoffmann-La Roche Ltd, Basel, CH-4070, Switz.
SOURCE:                  Bioorganic & Medicinal Chemistry Letters (2007),
                         17(5), 1307-1311
                         CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER:               Elsevier Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
OTHER SOURCE(S):         CASREACT 146:421892
GI
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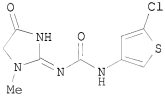
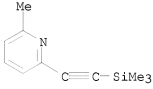


I

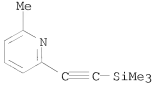
AB Optimization of affinity and microsomal stability led to identification of the potent, metabolically stable fenobam analog I. Robust in vivo efficacy of I was demonstrated in four different models of anxiety. Addnl., a ligand-based pharmacophore alignment of fenobam and MPEP was also proposed.

IT **656800-40-7**, 2-Methyl-6-[(trimethylsilanyl)ethynyl]pyridine
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of methyl(arylethynyl)pyridines or analogs thereof via Sonogashira cross-coupling reaction of methyl(silylethynyl)pyridine derivative with aryl iodides or iodopyridine and evaluation of their binding affinity for mGluR5 receptor)
RN 656800-40-7 CAPLUS
CN Pyridine, 2-methyl-6-[2-(trimethylsilyl)ethynyl]- (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:830277 CAPLUS
DOCUMENT NUMBER: 145:397337
TITLE: Structure-activity relationships for the linker in a series of pyridinyl-alkynes that are antagonists of the metabotropic glutamate receptor 5 (mGluR5)
AUTHOR(S): Bach, Peter; Nilsson, Karolina; Svensson, Tor; Bauer, Udo; Hammerland, Lance G.; Peterson, Alecia; Wallberg, Andreas; Oesterlund, Krister; Karis, David; Boije, Maria; Wensbo, David
CORPORATE SOURCE: Department of Medicinal Chemistry, AstraZeneca R&D Moelndal, Moelndal, S-431 83, Swed.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(18), 4788-4791
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:397337
AB Preparation and structure-activity relationships for the linker in a new series of metabotropic glutamate receptor 5 antagonists are presented together with in vitro and in vivo pharmacokinetic data.
IT **656800-40-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and structure-activity relationships for the linker in a series of arylalkynylpyridines that are antagonists of the metabotropic glutamate receptor 5 (mGluR5))
RN 656800-40-7 CAPLUS
CN Pyridine, 2-methyl-6-[2-(trimethylsilyl)ethynyl]- (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:386432 CAPLUS
DOCUMENT NUMBER: 144:425692
TITLE: Methods using TGF-β type I receptor inhibitors and Alk4 inhibitors for treating vascular injuries
INVENTOR(S): Ling, Leona E.; Fu, Kai; Gill, Alan; Gotwals, Philip J.
PATENT ASSIGNEE(S): Biogen Idec Ma Inc., USA
SOURCE: PCT Int. Appl., 228 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006044509	A2	20060427	WO 2005-US36770	20051013
WO 2006044509	A3	20060817		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2005295734	A1	20060427	AU 2005-295734	20051013
CA 2584248	A1	20060427	CA 2005-2584248	20051013
EP 1804801	A2	20070711	EP 2005-813747	20051013
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
JP 2008516962	T	20080522	JP 2007-536868	20051013
PRIORITY APPLN. INFO.:			US 2004-619116P P	20041015
			WO 2005-US36770 W	20051013

OTHER SOURCE(S): MARPAT 144:425692

AB The invention discloses the use of TGF-β type I receptor inhibitors and Alk4 inhibitors and implantable devices including these compds. in treating, preventing, or reducing intimal thickening, vascular remodeling, restenosis (e.g., coronary, peripheral, carotid restenosis), vascular diseases, (e.g., organ transplant-related, cardiac, lung and renal), and hypertension (e.g., primary and secondary hypertension, systolic hypertension, pulmonary hypertension, and hypertension-induced vascular remodeling resulting in target organ damage).

IT **672932-46-6 672932-50-2 672932-51-3 672932-52-4 672932-53-5 672932-54-6 672932-55-7 672932-56-8**
RL: DEV (Device component use); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TGF-β type I receptor inhibitors and Alk4 inhibitors for treating vascular injuries)

RN 672932-46-6 CAPLUS
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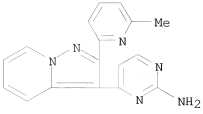
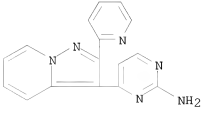
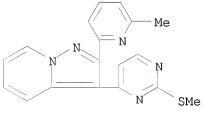
(CA INDEX NAME)



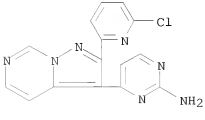
RN 672932-50-2 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(2-pyridinyl)pyrazolo[1,5-a]pyridin-3-yl]- (CA INDEX NAME)



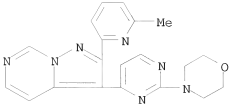
RN 672932-51-3 CAPLUS
CN Pyrazolo[1,5-a]pyridine, 2-(6-methyl-2-pyridinyl)-3-[2-(methylthio)-4-pyrimidinyl]- (CA INDEX NAME)



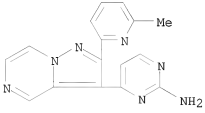
RN 672932-52-4 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(6-chloro-2-pyridinyl)pyrazolo[1,5-c]pyrimidin-3-yl]- (CA INDEX NAME)



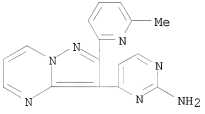
RN 672932-53-5 CAPLUS
CN Pyrazolo[1,5-c]pyrimidine, 2-(6-methyl-2-pyridinyl)-3-[2-(4-morpholinyl)-4-pyrimidinyl]- (CA INDEX NAME)



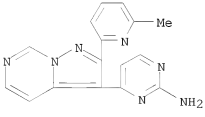
RN 672932-54-6 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(6-methyl-2-pyridinyl)pyrazolo[1,5-a]pyrazin-3-yl]-
(CA INDEX NAME)



RN 672932-55-7 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(6-methyl-2-pyridinyl)pyrazolo[1,5-a]pyrimidin-3-
yl]- (CA INDEX NAME)



RN 672932-56-8 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(6-methyl-2-pyridinyl)pyrazolo[1,5-c]pyrimidin-3-
yl]- (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2005:426434 CAPLUS
DOCUMENT NUMBER: 142:481950
TITLE: Preparation of phenylthioalkyl or phenylaminoalkyl pyridinylalkynes for treating gestroesophageal reflux disease (GERD)
INVENTOR(S): Bach, Peter; Bauer, Udo; Nilsson, Karolina; Wallberg, Andreas
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; NPS Pharmaceuticals, Inc.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005044267	A1	20050519	WO 2004-US34519	20041020
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2549969	A1	20050519	CA 2004-2549969	20041020
EP 1677790	A1	20060712	EP 2004-795655	20041020
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CN 1871002	A	20061129	CN 2004-80031087	20041020
JP 2007509935	T	20070419	JP 2006-538085	20041020
IN 2006DN02551	A	20070824	IN 2006-DN2551	20060505

PRIORITY APPLN. INFO.: US 2003-560713P P 20031031
US 2003-560714P P 20031031
WO 2004-US34519 W 20041020

OTHER SOURCE(S): CASREACT 142:481950; MARPAT 142:481950
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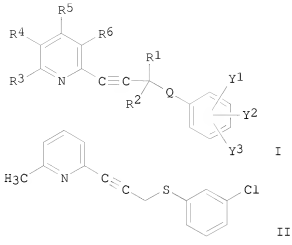


I

II

AB Title compds. I [wherein R1 = H, (cyclo)alkyl, (un)substituted (hetero)aryl; R2 = H or alkyl; R3 = H, alkyl, F, etc.; R4 = H, F, CF3, Me, etc.; R5, R6 = H or F; Q = (un)substituted S, NH or NCH3; Y1 - Y3 = H, halo, nitrile, etc., and pharmaceutically acceptable salts, hydrates, isoforms and/or optical isomers thereof] were prepared A synthetic process, i.e., coupling of the corresponding bromopyridines with propargyl alcs. [CH.tplbond.C-C(OH)R1R2] followed by mesylation of the resultant alcs. and subsequent substitution with anilines or benzenethiols, is claimed. Some intermediates involved in this method are also claimed. For example, II was prepared in several steps and had IC50 of 118 nM in the FLIPR assay using cells expressing human mGluR5d. Therefore, the invented compds. and their pharmaceutical compns. are useful for the treatment or prevention of gastroesophageal reflux disease (GERD).

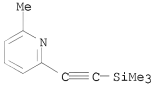
IT **656800-40-7P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of phenylthioalkyl or phenylaminoalkyl pyridinylalkynes for treating gestroesophageal reflux disease (GERD))

RN 656800-40-7 CAPLUS

CN Pyridine, 2-methyl-6-[2-(trimethylsilyl)ethynyl]- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2005:426433 CAPLUS

DOCUMENT NUMBER: 142:481949

TITLE: Preparation of phenylalkyl pyridinyl alkynes for treating gestroesophageal reflux disease (GERD)

INVENTOR(S): Bach, Peter; Bauer, Udo; Nilsson, Karolina; Wallberg, Andreas

PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; NPS Pharmaceuticals, Inc.

SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005044266	A1	20050519	WO 2004-US34517	20041020
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2549967	A1	20050519	CA 2004-2549967	20041020
EP 1677789	A1	20060712	EP 2004-795653	20041020
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CN 1870999	A	20061129	CN 2004-80030870	20041020
JP 2007510645	T	20070426	JP 2006-538084	20041020
IN 2006DN02552	A	20070824	IN 2006-DN2552	20060505

PRIORITY APPLN. INFO.: US 2003-560715P P 20031031
WO 2004-US34517 W 20041020
OTHER SOURCE(S): CASREACT 142:481949; MARPAT 142:481949
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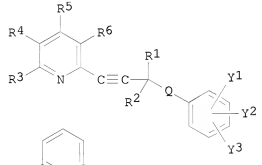

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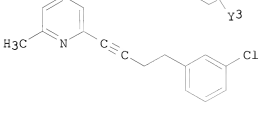


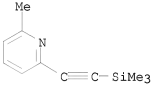
II

AB Title compds. I [wherein R1 = H, (cyclo)alkyl, (un)substituted (hetero)aryl; R2 = H or alkyl; R3 = H, alkyl, F, etc.; R4 = H, F, CF3, Me, etc.; R5, R6 = H or F; Q = (un)substituted alkyl or alkoxy, Y1 - Y3 = H, halo, nitrile, etc., and pharmaceutically acceptable salts, hydrates, isoforms and/or optical isomers thereof] were prepared A synthetic process,

i.e., Sonogashira coupling of the corresponding bromopyridines with monosubstituted alkynes, is claimed. The alkyne intermediates involved in this method are also claimed. For example, II was prepared via Pd-catalyzed coupling of 2-bromo-6-methylpyridine with 1-(3-butyn-1-yl)-3-chlorobenzene (preparation given) in 34% yield, and showed 31% inhibition at a dose of 4 μmol/kg/h (infusion during 60 min) in the barostat model assay in dogs. Therefore, the invented compds. and their pharmaceutical compns. are useful for the treatment of gastroesophageal reflux disease (GERD).

IT **656800-40-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of phenylalkyl pyridinyl alkynes for treating gestroesophageal reflux disease (GERD))

RN 656800-40-7 CAPLUS
CN Pyridine, 2-methyl-6-[2-(trimethylsilyl)ethynyl]- (CA INDEX NAME)

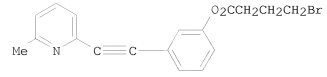


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

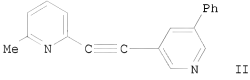
L4 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	2005:86385 CAPLUS
DOCUMENT NUMBER:	142:336223
TITLE:	Functionalization at position 3 of the phenyl ring of the potent mGluR5 noncompetitive antagonists MPEP
AUTHOR(S):	Alagille, David; Baldwin, Ronald M.; Roth, Bryan L.; Wroblewski, Jarda T.; Grajkowska, Ewa; Tamagnan, Gilles D.
CORPORATE SOURCE:	Yale University and VA Connecticut, Department of Psychiatry, West Haven, CT, 06516, USA
SOURCE:	Bioorganic & Medicinal Chemistry Letters (2005), 15(4), 945-949 CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER:	Elsevier B.V.
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 142:336223

GI



I



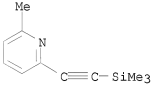
II

AB Synthesis and biol. evaluation of MPEP analogs functionalized at the position 3 of the Ph or pyridyl ring, e.g. I, II, are described. The key intermediates in the synthesis were 3-[(6-methyl-2-pyridinyl)ethynyl]phenol and 2-methyl-6-[(trimethylsilyl)ethynyl]pyridine. The results point out the limitation in the choice of a functional group at this position; the only substituents leading to retention of activity are NO2 (IC50 = 13 nM) and CN (IC50 = 8 nM).

IT **656800-40-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of MPEP analogs functionalized at position 3 of the Ph or pyridyl ring and their activity as mGluR5 antagonists)

RN 656800-40-7 CAPLUS

CN Pyridine, 2-methyl-6-[2-(trimethylsilyl)ethynyl]- (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:1043368 CAPLUS

DOCUMENT NUMBER: 142:106558

TITLE: Synthesis and receptor assay of aromatic-ethynyl-aromatic derivatives with potent mGluR5 antagonist activity

AUTHOR(S): Alagille, David; Baldwin, Ronald M.; Roth, Bryan L.; Wroblewski, Jarda T.; Grajkowska, Ewa; Tamagnan, Gilles D.

CORPORATE SOURCE: Department of Psychiatry, Yale University and VA Connecticut, West Haven, CT, 06516, USA

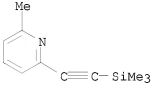
SOURCE: Bioorganic & Medicinal Chemistry (2004), Volume Date 2005, 13(1), 197-209
CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:106558

AB Noncompetitive antagonists of the human metabotropic glutamate receptor subtype 5 (mGluR5) have been implicated as potential therapeutics for the treatment of a variety of nervous system disorders, including pain, anxiety, and drug addiction. To discover novel noncompetitive antagonists to the mGluR5, the authors initiated an SAR study around the known lead compds. MPEP and M-MPEP. Our results pointed out the critical role of the para position of the two aromatic rings, which leads to inactive products and permitted the discovery of potent mGluR5 antagonists (e.g., 16, 25, 28, 34 IC50 = 13.5, 11.9, 21, 15 nM, resp.).

IT **656800-40-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and receptor assay of aromatic-ethynyl-aromatic derivs. with potent mGluR5 antagonist activity)

RN 656800-40-7 CAPLUS
CN Pyridine, 2-methyl-6-[2-(trimethylsilyl)ethynyl]- (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:220201 CAPLUS
DOCUMENT NUMBER: 140:270867
TITLE: Preparation of pyrazolopyridines as antagonists of Alk 5 and/or Alk 4
INVENTOR(S): Lee, Wen-cherng; Carter, Mary Beth; Sun, Lihong; Lyne, Paul; Chuaqui, Claudio; Zheng, Zhongli; Singh, Juswinder; Boriack-Sjodin, Paula
PATENT ASSIGNEE(S): Biogen, Inc., USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022054	A1	20040318	WO 2003-US27722	20030905

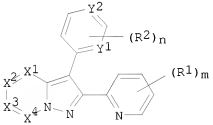
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2497970	A1	20040318	CA 2003-2497970		20030905
AU 2003268447	A1	20040329	AU 2003-268447		20030905
AU 2003268447	B2	20080724			
EP 1551398	A1	20050713	EP 2003-749412		20030905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003014053	A	20050719	BR 2003-14053		20030905
CN 1694698	A	20051109	CN 2003-824867		20030905
JP 2006502165	T	20060119	JP 2004-534571		20030905
NZ 539069	A	20070330	NZ 2003-539069		20030905
IN 2005DN00810	A	20070302	IN 2005-DN810		20050302
MX 2005002443	A	20050930	MX 2005-2443		20050303
ZA 2005001856	A	20060426	ZA 2005-1856		20050303
NO 2005001503	A	20050321	NO 2005-1503		20050321
US 20060106033	A1	20060518	US 2005-526839		20051101
PRIORITY APPLN. INFO.:			US 2002-408811P	P	20020906
			WO 2003-US27722	W	20030905

OTHER SOURCE(S): MARPAT 140:270867

GI



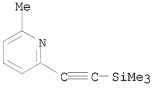
I

AB The title compds. [I; wherein each of X1-X4 is independently CRx or N; provided that only two of X1-X4 can be N simultaneously; each of Y1 and Y2 is independently CRy or N; provided that at least one of Y1 and Y2 must be N; R1 = alkyl, alkenyl, alkynyl, alkoxy, acyl, halo, hydroxy, amino, nitro, cyano, guanidino, amidino, carboxy, sulfo, mercapto, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, alkoxycarbonyl, alkylcarbonyloxy, urea, thiourea, sulfamoyl, sulfamide, carbamoyl, cycloalkyl, cycloalkyloxy, cycloalkylsulfanyl, heterocycloalkyl, heterocycloalkyloxy, etc.; R2 = alkyl, alkenyl, alkynyl, acyl, halo, hydroxy, NH2, NH(alkyl), N(alkyl)2, NH(cycloalkyl), N(alkyl)(cycloalkyl), NH(heterocycloalkyl), NH(heteroaryl), NH-alkylheterocycloalkyl, NH-alkylheteroaryl, NH(aralkyl), cycloalkyl, (cycloalkyl)alkyl, aryl, aralkyl, aroyl, heterocycloalkyl, (heterocycloalkyl)alkyl, etc.; m = an integer of 0-4; n = an integer of 0-3; provided that when m >2, two adjacent R1 or R2 groups can join together to form a 4- to 8-membered optionally substituted cyclic moiety; Rx, Ry = H, alkyl, alkenyl, alkynyl, alkoxy, acyl, halo, hydroxy, amino, nitro, cyano, guanidino, amidino, carboxy, sulfo, mercapto, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, cycloalkylcarbonyl, (cycloalkyl)alkylcarbonyl, aroyl, aralkylcarbonyl, etc.] or pharmaceutically acceptable salts or N-oxides thereof. These compds. possess unexpectedly high affinity for transforming growth factor β (TGFβ) type I receptor (Alk 5) and/or activin receptor type I (Alk 4), and can be useful as antagonists thereof for preventing and/or treating numerous diseases, including fibrotic disorders or diseases or

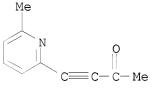
disorders mediated by an overexpression of TGFβ. The fibrotic condition is selected from the group consisting of scleroderma, lupus nephritis, connective tissue disease, wound healing, surgical scarring, spinal cord injury, CNS scarring, acute lung injury, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, acute lung injury, drug-induced lung injury, glomerulonephritis, diabetic nephropathy, hypertension-induced nephropathy, hepatic or biliary fibrosis, liver cirrhosis, primary biliary cirrhosis, fatty liver disease, primary sclerosing cholangitis, restenosis, cardiac fibrosis, opthalmic scarring, fibrosclerosis, fibrotic cancers, fibroids, fibroma, fibroadenomas, fibrosarcomas, transplant arteriopathy, and keloid. The diseases or disorders mediated by an overexpression of TGFβ are selected from the group consisting of demyelination of neurons in multiple sclerosis, Alzheimer's disease, cerebral angiopathy, squamous cell carcinomas, multiple myeloma, melanoma, glioma, glioblastomas, leukemia, and carcinomas of the lung, breast, ovary, cervix, liver, biliary tract, gastrointestinal tract, pancreas, prostate, and head and neck.

IT **656800-40-7P**, 2-Methyl-6-trimethylsilanylethynylpyridine
672932-47-7P, 4-(6-Methylpyridin-2-yl)-3-butyn-2-one
672932-48-8P, 1-[2-(6-Methylpyridin-2-yl)pyrazolo[1,5-a]pyridin-3-yl]ethanone **672932-49-9P**,
3-Dimethylamino-1-[2-(6-methylpyridin-2-yl)pyrazolo[1,5-a]pyridin-3-yl]propenone
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of pyrazolopyridines as antagonists of Alk 5 and/or Alk 4 for treating fibrotic disorders or diseases or disorders mediated by an overexpression of TGFβ)

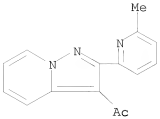
RN 656800-40-7 CAPLUS
CN Pyridine, 2-methyl-6-[2-(trimethylsilyl)ethynyl]- (CA INDEX NAME)



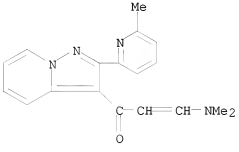
RN 672932-47-7 CAPLUS
CN 3-Butyn-2-one, 4-(6-methyl-2-pyridinyl)- (CA INDEX NAME)



RN 672932-48-8 CAPLUS
CN Ethanone, 1-[2-(6-methyl-2-pyridinyl)pyrazolo[1,5-a]pyridin-3-yl]- (CA INDEX NAME)

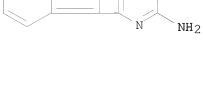


RN 672932-49-9 CAPLUS
CN 2-Propen-1-one, 3-(dimethylamino)-1-[2-(6-methyl-2-pyridinyl)pyrazolo[1,5-a]pyridin-3-yl]- (CA INDEX NAME)

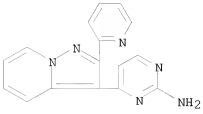


IT **672932-46-6P**, [4-[2-(6-Methylpyridin-2-yl)pyrazolo[1,5-a]pyridin-3-yl]pyrimidin-2-yl]amine **672932-50-2P**, [4-(2-Pyridin-2-ylpyrazolo[1,5-a]pyridin-3-yl)pyrimidin-2-yl]amine **672932-51-3P**, 2-(6-Methylpyridin-2-yl)-3-(2-methylsulfanylpyrimidin-4-yl)pyrazolo[1,5-a]pyridine **672932-52-4P**, [4-[2-(6-Chloropyridin-2-yl)pyrazolo[1,5-c]pyrimidin-3-yl]pyrimidin-2-yl]amine **672932-53-5P**, 2-(6-Methylpyridin-2-yl)-3-(2-morpholin-4-ylpyrimidin-4-yl)pyrazolo[1,5-c]pyrimidine **672932-54-6P**, [4-[2-(6-Methylpyridin-2-yl)pyrazolo[1,5-a]pyrazin-3-yl]pyrimidin-2-yl]amine **672932-55-7P**, [4-[2-(6-Methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl]pyrimidin-2-yl]amine **672932-56-8P**, [4-[2-(6-Methylpyridin-2-yl)pyrazolo[1,5-c]pyrimidin-3-yl]pyrimidin-2-yl]amine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazolopyridines as antagonists of Alk 5 and/or Alk 4 for treating fibrotic disorders or diseases or disorders mediated by an overexpression of TGFβ)

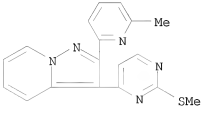
RN 672932-46-6 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(6-methyl-2-pyridinyl)pyrazolo[1,5-a]pyridin-3-yl]- (CA INDEX NAME)



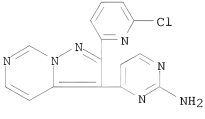
RN 672932-50-2 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(2-pyridinyl)pyrazolo[1,5-a]pyridin-3-yl]- (CA INDEX NAME)



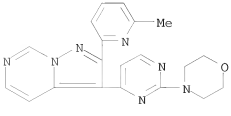
RN 672932-51-3 CAPLUS
CN Pyrazolo[1,5-a]pyridine, 2-(6-methyl-2-pyridinyl)-3-[2-(methylthio)-4-pyrimidinyl]- (CA INDEX NAME)



RN 672932-52-4 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(6-chloro-2-pyridinyl)pyrazolo[1,5-c]pyrimidin-3-yl]- (CA INDEX NAME)

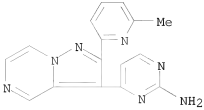


RN 672932-53-5 CAPLUS
CN Pyrazolo[1,5-c]pyrimidine, 2-(6-methyl-2-pyridinyl)-3-[2-(4-morpholinyl)-4-pyrimidinyl]- (CA INDEX NAME)



RN 672932-54-6 CAPLUS

CN 2-Pyrimidinamine, 4-[2-(6-methyl-2-pyridinyl)pyrazolo[1,5-a]pyrazin-3-yl]-
(CA INDEX NAME)



RN 672932-55-7 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(6-methyl-2-pyridinyl)pyrazolo[1,5-a]pyrimidin-3-
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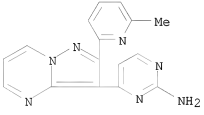
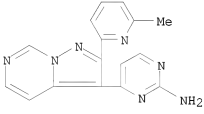


RN 672932-56-8 CAPLUS
CN 2-Pyrimidinamine, 4-[2-(6-methyl-2-pyridinyl)pyrazolo[1,5-c]pyrimidin-3-
yl]- (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:120851 CAPLUS
DOCUMENT NUMBER: 140:181331
TITLE: Preparation of 2-phenylpyridin-4-yl heterocycles as
selective activin-like kinase-5 inhibitors useful
against fibrosis and other disorders
INVENTOR(S): Dodic, Nerina; Gellibert, Francoise Jeanne
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004013135	A1	20040212	WO 2003-EP8496	20030729
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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AU 2003260345	A1	20040223	AU 2003-260345	20030729
EP 1539748	A1	20050615	EP 2003-766385	20030729
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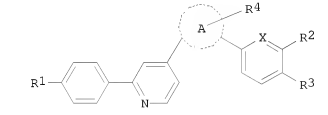
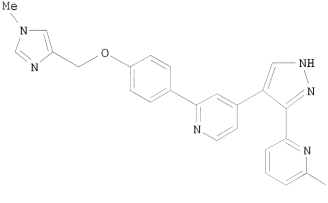
JP 2005539000	T	20051222	JP 2004-525405	20030729
US 20050245520	A1	20051103	US 2005-522969	20050131
PRIORITY APPLN. INFO.:			GB 2002-17751 A	20020731
			GB 2003-14698 A	20030624
			WO 2003-EP8496 W	20030729

OTHER SOURCE(S): MARPAT 140:181331

GI



I



II

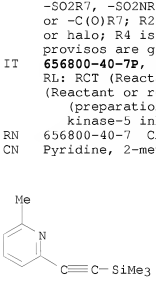
AB This invention relates to novel 2-phenylpyridin-4-yl heterocycles (shown as I; variables defined below; e.g. II) that are inhibitors of the transforming growth factor, ('TGF')-β signaling pathway, in particular, the phosphorylation of Smad-2 or Smad-3 by the TGF-β type I or activin-like kinase ('ALK')-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a

disease state mediated by this pathway, e.g. fibrosis (no data). All examples of I show ALK-5 receptor modulator activity (having IC50 values at 0.4-275 nM) and TGF-β cellular activity (having IC50 values at 0.001-10 μM). 4-[4-[4-[2-tert-Butyl-5-(6-methylpyridin-2-yl)-1H-imidazol-4-yl]pyridin-2-yl]phenyl]morpholine showed an ALK-5 receptor modulator activity of 34 nM and TGF-β cellular activity of 183 nM. N-(tetrahydropyran-4-yl)-4-[4-[2-isopropyl-5-(6-methylpyridin-2-yl)-1H-imidazol-4-yl]pyridin-2-yl]benzamide showed an ALK-5 receptor modulator activity of 25 nM and TGF-β cellular activity of <14 nM. Although the methods of preparation are not claimed, >150 example prepns. of I and .apprx.130 example prepns. of intermediates are included. For example, II was prepared in 37% yield by reacting 4-[4-[3-(6-methylpyridin-2-yl)-1-trityl-1H-pyrazol-4-yl]pyridin-2-yl]phenol and NaH in DMF with 1-methyl-4-hydroxymethylimidazole followed by removal of the trityl group using HCl in MeOH; details are also given for preparation of the reactants. For I: A is furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiadiazole, benzofuran, indole, isoindole, indazole, imidazopyridine, quinazoline, quinoline, isoquinoline, pyrazole or triazole; X is N or CH; R1 is H, C1-6alkyl, C1-6alkenyl, C1-6alkoxy, halo, cyano, perfluoro C1-6alkyl, perfluoroC1-6alkoxy, -NR5R6, -(CH2)nNR5R6, -O(CH2)nOR7, -O(CH2)n-Het, -O(CH2)nNR5R6, -CONR5R6, -CO(CH2)nNR5R6, -SO2R7, -SO2NR5R6, -NR5SO2R7, -NR5COR7, -O(CH2)nCONR5R6, -NR5CO(CH2)nNR5R6 or -C(O)R7; R2 is H, C1-6alkyl, halo, cyano or perfluoroC1-6alkyl; R3 is H or halo; R4 is H, halo, Ph, C1-6alkyl or -NR5R6; addnl. details including provisos are given in the claims.

IT **656800-40-7P**, 2-Methyl-6-[(trimethylsilanyl)ethynyl]pyridine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 2-phenylpyridin-4-yl heterocycles as selective activin-like kinase-5 inhibitors useful against fibrosis and other disorders)

RN 656800-40-7 CAPLUS

CN Pyridine, 2-methyl-6-[2-(trimethylsilyl)ethynyl]- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:120845 CAPLUS

DOCUMENT NUMBER: 140:163879

TITLE: Pyridinyl-substituted [1,2,3]triazoles as inhibitors of the TGF-β signalling pathway, and their preparation and use in medicine as ALK-5 receptor modulators

INVENTOR(S): Gellibert, Francoise Jeanne

PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA

SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004013125	A1	20040212	WO 2003-EP8386	20030729
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003260337	A1	20040223	AU 2003-260337	20030729
EP 1530567	A1	20050518	EP 2003-766353	20030729
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005538997	T	20051222	JP 2004-525373	20030729
US 20060074244	A1	20060406	US 2005-522966	20050131
PRIORITY APPLN. INFO.:			GB 2002-17780 A	20020731
			WO 2003-EP8386 W	20030729

OTHER SOURCE(S): CASREACT 140:163879; MARPAT 140:163879
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

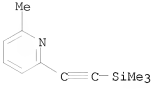
AB The invention relates to novel triazole derivs. I, which are inhibitors of the transforming growth factor, TGF-β signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF-β type I or activin-like kinase ('ALK')-5 receptor [wherein: X = N, CH; R1 = H, alkyl, alkenyl, alkoxy, halo, cyano, perfluoroalkyl or -alkoxy, NR4R5, (CH2)nNR4R5, O(CH2)nOR6, O(CH2)nNR4R5, CONR4R5, CO(CH2)nNR4R5, SO2R6, SO2NR4R5, NR5SO2R6, NR4COR6; R2 = H, alkyl, halo, cyano, or perfluoroalkyl; R3 = H or halo; R4, R5 = H, alkyl, or Het; or NR4R5 = 3- to 7-membered (un)saturated ring with ≥1 N/O/S atom(s) and optionally substituted by ≥1 halo, cyano, CF3, OH, OCF3, alkyl, and/or alkoxy; R6 = H or alkyl; Het = 5- or 6-membered, C-linked, (un)saturated or aromatic N/O/S heterocycle optionally substituted by alkyl; n = 1-4]. The invention also relates to methods for the preparation of I, and their use in medicine, specifically in the treatment and prevention of disease states mediated by the TGF-β signaling pathway. Claimed uses include treatment or prophylaxis of disorders mediated by the ALK5 receptor, including a variety of specific diseases, particularly kidney fibrosis. Ten specific compds. I are described in examples and claimed by name. Examples also include a variety of intermediates. For instance, 4-amino-2-chloropyridine was diazotized and iodinated (63%), then coupled with 2-ethynyl-6-methylpyridine (preparation given) to give 86.4% of the diheteroarylalkyne intermediate II. Palladium-catalyzed arylation of II by 4-(MeSO2)C6H4B(OH)2 (46%) and triazole formation via cycloaddn. with azidotrimethylsilane and hydrolysis (33.2%) gave invention compound III. In two in-vitro expts. using recombinant targets, all exemplary compds. I showed ALK5 receptor modulator activity with IC50 values of 1-200 nM (e.g., 26 nM for III), and TGF-β cellular activity with IC50 values of 0.001 μM to 10 μM (e.g., 413 nM for III).

IT **656800-40-7P**, 2-Methyl-6-[(trimethylsilanyl)ethynyl]pyridine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(intermediate; preparation of pyridinyl-substituted triazoles as inhibitors of TGF-β signaling pathway and ALK-5 receptor modulators)

RN 656800-40-7 CAPLUS

CN Pyridine, 2-methyl-6-[2-(trimethylsilyl)ethynyl]- (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT